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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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AMERICAN HOME PRODUCTS CORPORATION
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MADISON, NJ 07940

EXAMINER

TURNER, SHARON L

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 12/13/2001

26

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/007,385

Applicant(s)

Hsien-Jue

Examiner

Sharon L. Turner, Ph.D.

Art Unit

1647



– The MAILING DATE of this communication appears on the cover sheet with the corresponding address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 10-1-01

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1035 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 2, 5-8, and 10-21 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 2, 5-8, and 10-21 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirements.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

19) ☐ Notice of Informal Patent Application (PTO-152)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

20) ☐ Other: _____

Art Unit: 1647

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-01-01 has been entered.
2. The amendment and declaration filed 6-29-01 has been entered into the record and has been fully considered.
3. Claims 3, 4 and 9 are canceled. Claims 2, 5-8, and 10-21 are pending.
4. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

Claim Objections

5. Claims 10, 15 and 17 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 does not further limit the composition as no amount or dosage form is specified. Claims 15 and 17 do not further limit the composition but instead recite methods of administration.

Art Unit: 1647

6. Claims 12-13 are objected to because of the following informalities: It is suggested for clarity that claims 12 and 13 be amended to indicate colony forming units (CFU) as the relative unit of administration.

Claim Rejections - 35 USC § 112

7. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 depends on claim 11 and thus incorporates the limitations of claims 10 and 2, yet claim 2 recites a single composition whereas claim 14 appears to recite two separate compositions. Clarification of the composition(s) and/or form is required.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 2, 5-8 and 10-21 stand rejected under 35 U.S.C. 103(a) as set forth in Paper No. 15 and 18 mailed 5-4-00 and 1-3-01, as being unpatentable over US Patent No. 5,183,659, Timoney et al, 2 February, 1993, in view of EP0786518 A1, Hartford et al, 24 January 1997, and US Patent No. 5,597,807, Estrada et al., 28 January 1997 as further evidenced by Timoney et al., Recent advances in streptococci and streptococcal diseases (1985) pp. 294-5, Proceed. Of the

Art Unit: 1647

IXth Lancefield Int'l Symp. on Strep. and Strep. Diseases, Japan, September 1984, Reedbooks Ltd., Chertsey.

Applicant's arguments and declaration filed 6-29-01 have been fully considered but they are not persuasive.

In paragraphs 1-2 of the traversal Applicants argue that Timoney is silent as to adjuvants and thus it is not obvious from Timoney to use saponin as an adjuvant. Applicant's argue that absence a suggestion that the adjuvant saponin has immunostimulatory properties and that such an adjuvant would provide a protective immune response to challenge to disease one would not be motivated to modify Timoney to arrive at the invention.

In response, Hartford suggests that the adjuvant saponin has immunostimulatory properties such that it provides a protective immune response against disease challenge. In particular, Hartford teaches protection via a live attenuated nasal mucosa *S. equi* vaccine in combination with an immunostimulant which comprises Quil A (saponin) adjuvant to enhance the immune response of the host to the invading pathogen, see in particular p. 3, lines 39-46.

In paragraph 3 of the traversal Applicants argue that Hartford and Estrada do not remedy the deficiencies of Timoney, in particular that Quil A (saponin) is but one adjuvant included in the deletion vaccine of Hartford but that such adjuvant is not exemplified. Applicant's argue that Hartford does not teach or suggest that any adjuvant *stimulates* mucosal immunity and does not teach or suggest that Quil A is an immunostimulatory adjuvant.

Art Unit: 1647

In response, Hartford does teach that Quil A is a known adjuvant which stimulates the immune system and enhances the immune response of the host, see in particular p. 3, lines 39-46. In addition, Estrada specifically teaches that saponins Quillaja and Quinoa stimulate IgG and IgA, mucosal specific immunity, see in particular Estrada, Figures 1-6, and columns 5-8.

In paragraph 4 of the traversal Applicants argue that Estrada also fails in that *Quinoa* saponin is but one specific type of saponin that surprisingly stimulates an immune response when administered mucosally, but that Estrada does not use *S. equi* or a comparable antigen and thus Estrada does not teach or suggest that an immune response may be achieved using the combination of *Quinoa* saponin and *S. Equi* or a comparable bacterial or disease causing antigen. Applicants further argue that neither does Estrada teach that Quinoa saponin provides protection from infection in the face of challenge.

In response, Estrada is not solely relied upon for such teachings. It is Hartford and Estrada which in particular cumulatively teach that Quillaja (Quil A) and Quinoa saponins are effective in stimulating immunity including mucosal immunity as evidenced by production of IgG and IgA as exemplified in Estrada and in promoting *S. equi* specific immune responses as is taught by Estrada, column 5, line 36-column 6, line 52 and Hartford p. 3, lines 39-46, Examples 1-IV, Results and also the Conclusion.

In paragraphs 5-8 of the traversal Applicants argue that Estrada's teachings are unexpectedly different than Quil A saponin and thus that there is no reasonable expectation that such adjuvants would provide an enhanced immune response or protection in horses. Applicants

Art Unit: 1647

acknowledge that Estrada teaches Quinoa saponin increased IgG and IgA, however they subsequently argue that such an immunological response is not predictive of protective immunity in the face of challenge. Applicants submit that the artisan knows that there is no definite correlation between the presence of antibodies and protective immunity as demonstrated in the specification at pp. 15-16 of the specification and that if the levels are not predictive then there is no expectation of enhanced protective effect with adjuvant. Applicants acknowledge that Estrada causes increased absorption through mucosal membranes but argue that the reference does not teach or suggest that saponin stimulates protective mucosal immunity in challenge and thus that there is no reasonable prediction of protection provided by immunization with Quinoa saponins.

In response, it is unclear how Estrada's teachings are still considered unexpected with respect to Quil A as Estrada notes IgG and IgA production via Quillaja and Quinoa saponins. While Estrada notes that IgA responses had not yet been noted for Quillaja, Estrada clearly shows that as of at least 1-28-1997 IgA and IgG stimulation are known for Quillaja and Quinoa saponins and would not be unexpected as of the filing date of instant '385, 1-15-1998. Applicant's arguments with respect to the predictability of the immune response in response to challenge is jointly addressed in Timoney, Hartford and Estrada. For example, instantly claimed vaccine (live non-encapsulated attenuated *S. equi*) is the same as Timoney with the sole exception of saponin adjuvant. Timoney has already established in the art that the claimed live non-encapsulated attenuated *S. equi* vaccine stimulates the appropriate immune responses such that protective immunity is established in the host in response to challenge, including IgG and

Art Unit: 1647

IgA even without adjuvant, see in particular Figures 1-3, Columns 5-6 and Claims 1-10. Thus, the specificity of the vaccine is established. It is known in the art as exemplified by Hartford and Estrada that Quillaja and Quinoa saponins are adjuvants which enhance antigen specific immune responses in the host when co-administered with the appropriate antigens, and that saponins predictably and specifically stimulate mucosal immunity through enhanced mucosal absorption and production of antigen specific IgG and IgA, see in particular Hartford, p. 3 and Estrada, columns 5-6, as noted above. Thus, the predictive effects do not appear to be of question. It is also noted that sero conversion per. se., is not required but merely IgG and/or IgA mucosal production. The artisan would expect only improved vaccination effects by inclusion of a saponin adjuvant with the Timoney vaccine, the specificity of the vaccine already having been established by Timoney.

In paragraph 9 of the traversal Applicants argue that Estrada does not teach the use of *S. equi* or other bacterial or disease causing antigens but that Estrada uses avidin and cholera toxin which are known adjuvants as exemplified by Hartford, p. 3, lines 39-44. Applicants conclude that thus Estrada teaches non-specific immunological responses to adjuvants by administration of saponin and that the artisan could not predict protection against contact with a specific disease based on Estrada's teachings.

In response, it is not Estrada's teachings which are solely relied upon, but the cumulative teachings of Timoney, Hartford and Estrada as set forth above.

Art Unit: 1647

In paragraphs 10-11 of the traversal Applicants argue that the artisan could not predict a protective immune response using any saponin type, in particular as Estrada teaches the benefits of Quinoa saponin which are unexpectedly different from Quillaja saponin. Applicants again argue that Estrada fails to use disease specific antigen and that Quinoa saponins rather than Quillaja saponins enhance nonspecific immunity and cause increased absorption through mucosal membranes. Evidence of unexpectedness is noted at col. 2, lines 25-27 and that thus the artisan could not expect the properties of any type of saponin used as an adjuvant. Based on the aforementioned teachings Applicants conclude that Estrada does not supply the suggestion or motivation missing from Hartford and Timoney to render the invention obvious.

In response, as noted above Estrada is not unexpected as of the patent publication date. The benefits of Quillaja and Quinoa saponins in the stimulation of enhanced mucosal immunity as exemplified by enhanced mucosal absorption, IgG and IgA production are noted in Estrada. The specificity of the Timoney vaccine is established. Hartford also suggests the inclusion of adjuvants for enhancing the immune response in *S. equi* vaccination of animals, and specifically for mucosal immunity. Thus, Estrada and Hartford both provide suggestion and motivation to modify the Timoney vaccine by inclusion of saponin adjuvants.

In paragraphs 12-15, Applicants note the Examiner's previous assertion that Timoney at col. 6, lines 30-31 teach that "the mouse has historically been the model for the immunology of *S. equi* infection." However, Applicants conclude that all this teaches is the study of the immune response in mice to potential equine vaccines. Applicants argue that Timoney did not extrapolate

Art Unit: 1647

the data in mice to conclude or suggest a similar effect in horses. Applicants argue that Hartford did not establish protective effects in horses, but only in mice using the mouse model.

Applicants again suggest that Hartford did not extrapolate or suggest similar effect in horses.

Applicants further argue that even though Hartford did test the vaccine in horses, the test was only for safety and not efficacy, and that the artisan could not conclude efficacy without actually performing the tests in horses. Applicants argue that the Examiner's conclusion of intrinsic immunity is not supported by the reference teachings and is constructed by hindsight reasoning and that the artisan could, at best only be motivated to combine Hartford, Estrada and Timoney based on the present invention because Timoney is silent to adjuvants which would provide the enhanced protective immunological effect demonstrated by the claimed saponin and the attenuated *S. equi* vaccine.

In response, it is noted that Timoney not only suggests that the mouse model is capable of extrapolation to horses, Timoney shows that it is extrapolatable by showing that the protective effects in horses are indeed exemplified in mice. In particular, Timoney directly compares in a "parallel test of efficacy" horses and mice, see in particular column 5, line 7-column 6, line 5 and column 6, line 29-line 54. Hartford also includes experimentation in mice, and horses.

Hartford's safety, treatment, vaccination/challenge and protection studies are directed to both mice and horse vaccines, but are especially contemplated for use in treatment of horses, see in particular p. 2, lines 1-49 and p. 3, lines 6-10, "the invention further provides a live vaccine for combating Streptococcus infection in horses." In addition, to the experimentation in mice, (see

Art Unit: 1647

in particular Examples III-IV), Example V, teaches that the protective results noted in mice are comparable those noted in horses. In particular, six horses were inoculated and followed to 4 weeks post/challenge. No mortality nor clinical signs of infection were noted, in particular there were no sudden temperatures nor abscesses formed in the mandibular and pharyngeal lymph nodes, see in particular p. 12, Clinical signs and Post-mortem examination. Thus, the prevailing evidence of the references establishes, even in the safety studies of Hartford, that prior to Applicant's invention, the *S. equi* vaccines or the prior art were known to be similarly protective and predictive in both horse and mouse models as disclosed.

Finally, in paragraph 16-20, Applicants point to the declaration of 6-29-01 and conclude therefrom that the invention is thus not obvious in light of Timoney, Hartford and Estrada, alone or in combination. In particular, that the prior art fails to render obvious that the *S. equi* vaccine when combined with saponin, would exhibit enhanced immunostimulatory and protective effects as a result of the addition of saponin.

Applicant's declaration filed 6-29-01 has been fully considered but is not persuasive. In particular, the Examiner notes that the comparison delineated in the declaration is between the instantly claimed vaccination and a commercial vaccine of Carbopol/*S. equi* enzyme extract administered intra-muscularly. Such evidence is insufficient to show an unexpected difference in the vaccine of Timoney and the vaccine of Timoney when modified by the inclusion of saponin, particularly as the Timoney, Hartford and Estrada reference teachings cumulatively suggest that the saponins' inclusion would specifically enhance the protective immune response stimulated by

Art Unit: 1647

the Timoney vaccine alone. Additionally, it is noted that there is no evidence of record which would contradict the efficacy of any adjuvant or of saponin in particular from exhibiting such effects, in particular as noted for the benefits of mucosal administration and immunity.

Although not relied on for the rejection, it is again noted that the skilled artisan recognizes as set forth in Timoney et al., Recent advances in streptococci and streptococcal diseases (1985) pp. 294-5, Proceed. Of the IXth Lancefield Int'l Symp. on Strep. and Strep. Diseases, Japan, September 1984, Reedbooks Ltd., Chertsey, that cumulative findings suggest that successful vaccination requires stimulation of the nasopharyngeal immune response and that vaccination with 709-27 stimulates IgA and IgG antibodies even in the absence of Q. Saponin adjuvant, see in particular Figure 1.

The references cumulatively provide both the suggestion of making the invention and an expectation of success. Therefore the claimed invention is rendered obvious to the skilled artisan at the time of the invention.

It is further noted that the amended language "for providing protective immunity against Streptococcus equi infection following Streptococcus equi challenge" is non-limiting to the composition and similarly contributes no further steps in any methods as recited in Claims 17-21. The limitation is akin to a recitation of intended use without the addition of further limiting active steps. However, to the extent to which the recitation implies that the method be administered "following Streptococcus equi challenge", it is unclear that applicants have support for such language as no support was provided by page and line number at the time of entry. For

Art Unit: 1647

search and examination purposes the recitation has received no weight. The recitation "for providing protective immunity against Streptococcus equi ingestion" is non-limiting but has been specifically addressed in the rejection above.

Status of Claims

10. No claims are allowed.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
December 11, 2001

**CHRISTINE J. SAOUD
PRIMARY EXAMINER**

Christine J. Saoud